Three-Component and Nonclassical Reaction of Phosphines with Enynes and Aldehydes: Formation of γ-Lactones Featuring α-Phosphorus Ylides
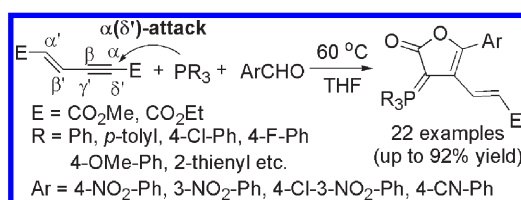
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ABSTRACT

Inverted carbenoid species, generated from attack of phosphines at the α(δ′)-carbon of hex-2-en-4-ynedioic acid dialkyl esters, react with aldehydes to give γ-lactones possessing an α-phosphorus ylide moiety.

Michael addition, a type of nucleophilic conjugate addition, is a well-known addition pattern that takes place in the reaction of α,β-unsaturated carbonyl compounds with nucleophilic reagents.[1] Chemists take this as a common methodology for the syntheses of a wide range of organic compounds for applications.[2] In parallel to this concept, this addition model has been used to account for the reaction outcomes of organophosphines with electron-deficient alkenes and alkynes.[3] This organophosphorus system can assemble molecules in a catalytic manner.[4] Asymmetric versions of such phosphine-catalysis[5] and

their synthetic applications have also been elaborated.[6] Recently, Fu,[7] Kwon,[8] and others[9] further demonstrated versatile reactions within this regime. The accepted mechanisms for these phosphine-mediated reactions with alkynes (1a) or allenoates (1b) have been proposed; in these studies, phosphines attack at the β-carbon of these substrates and form zwitterionic carbenoid species **A** or **B** followed by the subsequent steps (Scheme 1).

In our recent study, we find that [60]fullerene is a good electrophile for the carbenoid species generated from phosphines with dimethyl acetylenedicarboxylate (DMAD), resulting in a new class of cyclopropanofullerenes.[10] We

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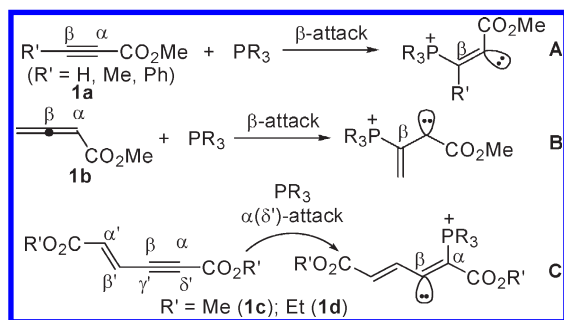(6) Wang, J. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855.

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Scheme 1

Table 1. Condition Optimization Study[a]

entry	solvent	time (h)	temp (°C)	yield (%)[b]
1[c]	THF	24	rt	43 (68)
2[c]	CH$_2$Cl$_2$	24	rt	21 (39)
3[c]	DCE[h]	3	60	32 (56)
4[c]	THF	3	60	35 (57)
5[c]	THF	5	60	37 (70)
6[c,d]	THF	3	60	21 (76)
7[e]	THF	3	60	46 (50)
8[f]	THF	3	60	69 (79)
9[g]	THF	24	rt	74
10[g]	THF	3	60	92
11[g]	CH$_2$Cl$_2$	24	rt	49
12[d,g]	THF	3	60	80

[a] Reaction was carried out under anhydrous condition unless otherwise noted. [b] Yields were determined by ^{1}H NMR with mesitylene as an internal standard and yields in parentheses were determined based on converted aldehydes. [c] Molar ratio of **1c**:**2a**:**3a** = 1:1:1. [d] With 1 equiv of H$_2$O as an additive. [e] Molar ratio of **1c**:**2a**:**3a** = 1.5:1:1. [f] Molar ratio of **1c**:**2a**:**3a** = 1.5:1.5:1. [g] Molar ratio of **1c**:**2a**:**3a** = 2:2:1. [h] 1,2-Dichloroethane.

think that desymmetrization of DMAD through insertion of an ethylenyl unit to give **1c**[11] will generate distinguishable alkynyl carbons; such enyne substrate gives unusual 1,3-dipolarophile **C** through attack of phosphines at the α(δ')-carbon (α relative to its proximate ester carbon and δ' relative to its farthest ester carbon) of the reactive alkyne. The unusual conjugate addition (α or δ' attack)[12] pattern was less being considered as a possible route for organic syntheses since such type of acceptors were rare.[13] Here we show that α(δ')-addition products dominate exclusively in the reaction of phosphines with enyne (**1c,d**) and aldehydes, unambiguously evidenced by X-ray crystallographic analyses and density functional theory (DFT) results.
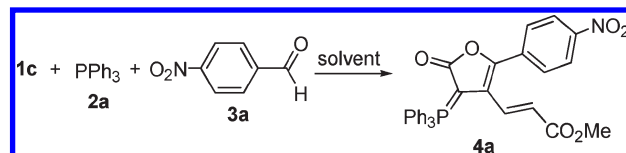
We first investigated the reaction conditions of **1c**, PPh$_3$ (**2a**), and 4-nitrobenzaldehyde (**3a**), providing novel lactone **4a**, in a 1:1:1 molar ratio (Table 1). We found that the reaction proceeded smoothly in THF at room temperature, giving 43% yield (68% based on converted **3a**), and was superior to that in CH$_2$Cl$_2$ (entries 1 and 2). The reaction proceeded to near completion at t = 3 h in THF at 60 °C (entries 4 and 5). Increasing the molar ratios of **1c** and **2a** with respect to **3a** gave higher yields: 46% and 69% yields respectively for ratios of 1.5:1:1 and 1.5:1.5:1 (entries 7 and 8). We found that a molar ratio of 2:2:1 for **1c**:**2a**:**3a** was optimal for full consumption of **3a**, giving 74% and 92% yields at room temperature and 60 °C, respectively (entries 9 and 10). Reactions performed poorly in chlorinated solvents as compared to those in THF (entries 2, 3, and 11). Finally, we observed that the reaction performance was deteriorated upon addition of 1 equiv of water (entries 6 and 12).

To gain insightful scope of this nonclassical addition, we next evaluated reactivity of various phosphines **2b**−**h** with

1c and **3a** (Table 2). We found that reactions with triarylphosphines generally gave moderate to good yields (55−79%; 62−88% based on converted aldehydes; entries 1−6). Phosphines with electron-releasing aryl groups (entries 1−3) outperformed those with electron-withdrawing moieties (entries 4 and 5). Heteroaryl phosphine (**2g**) also produced product **4g** with relatively lower yields (entry 6). Phosphine equipped with an alkyl group (**2h**) caused labile products; in this case, we could only isolate product **4h** incorporating PMePh$_2$ in 38% yield (entry 7). We further evaluated other substituted aldehydes **3b**−**d** or enyne **1d** with representative phosphines. We observed that reactions with 3-NO$_2$ (**3b**, entries 8−12), 4-Cl-3-NO$_2$ (**3c**, entries 13−15), and 4-CN (**3d**, entries 19−21) substituted aldehydes or enyne **1d** (entries 16−18) gave comparable yields at the same conditions. However, attempts at using more electron-rich aromatic aldehydes or aliphatic aldehydes did not give desirable products.[14]

We characterized the isolated compounds **4a**−**v** using infrared (IR) and ^{1}H, ^{13}C, and ^{31}P nuclear magnetic resonance (NMR) spectroscopy, electron-impact or electron-spray mass spectrometry (EI-MS or ESI), and X-ray crystallographic analyses. Some isolated compounds tend to crystallize upon slow evaporation of their dichloromethane solution. We obtained an X-ray crystal structure

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(14) Reactions with aldehydes, such as benzaldehyde, 4-*tert*-butylbenzaldehyde, 4-methylbenzaldehyde, 4-chlorobenzaldehyde, 4-fluorobenzaldehyde, 2,4-difluorobenzaldehyde, 4-methoxybenzaldehyde, and 1-butanal did not provide the corresponding products under the investigated conditions. In these reactions, polar dark-brown materials were obtained, likely due to polymerization of enynes.

Table 2. Reaction of **1c–d**, Phosphines **2**, and Aldehydes **3**[a]
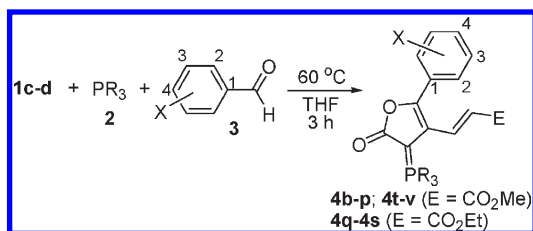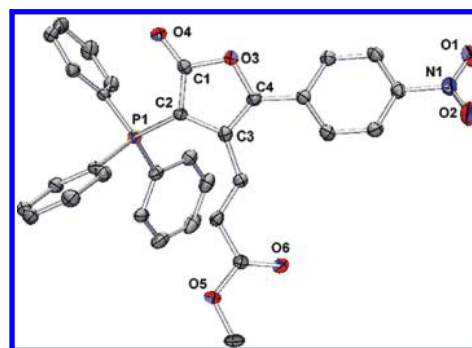

entry	enyne 1	phosphine PR$_3$ (2)	substituent X (3)	product 4	yield (%)[b]
1	1c	P(p-tolyl)$_3$ (2b)	4-NO$_2$ (3a)	4b	79 (88)
2	1c	PPh$_2$(p-tolyl) (2c)	4-NO$_2$ (3a)	4c	78
3	1c	P(4-OMe-Ph)$_3$ (2d)	4-NO$_2$ (3a)	4d	77
4	1c	P(4-Cl-Ph)$_3$ (2e)	4-NO$_2$ (3a)	4e	65 (76)
5	1c	P(4-F-Ph)$_3$ (2f)	4-NO$_2$ (3a)	4f	62 (66)
6	1c	P(2-thienyl)$_3$ (2g)	4-NO$_2$ (3a)	4g	55 (62)
7	1c	PMePh$_2$ (2h)	4-NO$_2$ (3a)	4h	38 (45)
8	1c	P(4-OMe-Ph)$_3$ (2d)	3-NO$_2$ (3b)	4i	66
9	1c	P(p-tolyl)$_3$ (2b)	3-NO$_2$ (3b)	4j	74(94)
10	1c	PPh$_2$(p-tolyl) (2c)	3-NO$_2$ (3b)	4k	81
11	1c	PPh$_3$ (2a)	3-NO$_2$ (3b)	4l	80
12	1c	P(4-Cl-Ph)$_3$ (2e)	3-NO$_2$ (3b)	4m	56 (71)
13	1c	P(4-OMe-Ph)$_3$ (2d)	4-Cl-3-NO$_2$ (3c)	4n	70
14	1c	PPh$_3$ (2a)	4-Cl-3-NO$_2$ (3c)	4o	76
15	1c	P(4-Cl-Ph)$_3$ (2e)	4-Cl-3-NO$_2$ (3c)	4p	59(67)
16	1d	P(p-tolyl)$_3$ (2b)	4-NO$_2$ (3a)	4q	68
17	1d	PPh$_3$ (2a)	4-NO$_2$ (3a)	4r	68
18	1d	P(4-Cl-Ph)$_3$ (2e)	4-NO$_2$ (3a)	4s	61 (64)
19	1c	P(4-OMe-Ph)$_3$ (2d)	4-CN (3d)	4t	72
20	1c	PPh$_3$ (2a)	4-CN (3d)	4u	68
21	1c	P(4-Cl-Ph)$_3$ (2e)	4-CN (3d)	4v	51 (57)

[a] Reaction was carried out under anhydrous condition unless otherwise noted; molar ratio of **1c–d**:**2**:**3** = 2:2:1. [b] Yields were determined by ^{1}H NMR with mesitylene as an internal standard and yields in parentheses were determined based on converted aldehydes.
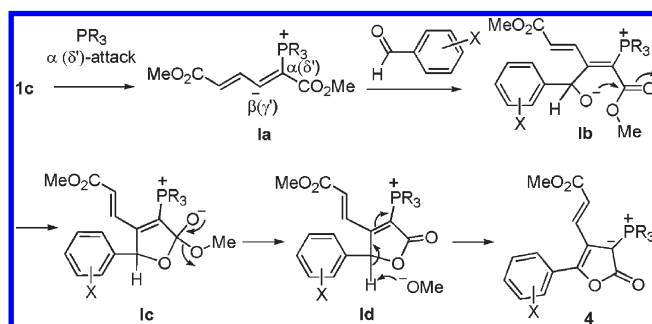

**Figure 1.** Thermal ellipsoids of compound **4a** drawn at the 30% level of probability.

deprotonation takes place to form product **4**. More electron-rich aromatic or aliphatic aldehydes may cause the C–H protons of **Id** to be less reactive for deprotonation and thus did not form lactone **4**.

Scheme 2. Mechanism for Formation of **4**

The formation of these nonclassical products led us to realize electronic properties of **1c**. We evaluated Mulliken charges and LUMO coefficients along the z-axis of **1c**. We found that the $\alpha(\delta')$-carbon, with Mulliken charge values of −0.018, 0.049, and 0.147 respectively, exhibited more positive charge density than the $\beta(\gamma')$-carbon, with values of −0.058, 0.000, and 0.032 using HF/6-31(G) and DFT at B3LYP/3-21G and B3LYP/6-31G(d) levels of theory (Table 3, entries 1−3).[16] This electropositive notion is also consistent with their experimental ^{13}C NMR chemical shifts, 86.7 and 81.8 ppm for the $\alpha(\delta')$ and $\beta(\gamma')$ carbons, respectively. We envisaged that absolute values of LUMO coefficients (2P$_z$) on $\alpha(\delta')$-carbon are larger that those of $\beta(\gamma')$-carbon along the z-axis of **1c** (entries 1−3). Hence, we conclude that the $\alpha(\delta')$-carbon is more susceptible to nucleophilic attack than the $\beta(\gamma')$-carbon on the basis of higher level theory results. Computed chemical shifts of $\alpha(\delta')$ and $\beta(\gamma')$ carbons corroborate with experimental ones (entry 4).

of compound **4a** (Figure 1).[15] The phosphorus atom (P1) clearly bonds to carbon (C2), the $\alpha(\delta')$-carbon of enyne **1c**, with a bond length of 1.7406(17) Å. Due to the delocalization of negative charge from ylidic carbon C2 to the carbonyl π bond (C1−O4), the C1−C2 bond is shorter (1.424(2) Å) than a lactone ring without an α-phosphorus ylide moiety. The P1 atom does not stay in the same plane with the lactone ring due to steric encumbrance, evidenced from the dihedral angle (ψO4−C1−C2−P1) of 17.6(3)°.

We account for the formation of ylide **4** by nucleophilic attack of phosphine PR$_3$ at the $\alpha(\delta')$-position of the enyne **1c** (Scheme 2), generating a reactive zwitterionic species **Ia** bearing a carbenoid moiety at the $\beta(\gamma')$-carbon. Addition of **Ia** to the carbonyl carbon of aldehydes followed by intramolecular cyclization gives **Ic** (via intermediate **Ib**). Then, a methoxide molecule is released. Finally,

(15) See the Supporting Information for spectroscopic assignment and X-ray data for compound **4a** (The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 818904. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html).

(16) Gaussian 09 program, see the Supporting Information (SI) for the full citation.

Table 3. Computed Mulliken Charges and LUMO Coefficients along z-Axis on $\alpha(\delta')$ and $\beta(\gamma')$ Carbons of **1c**
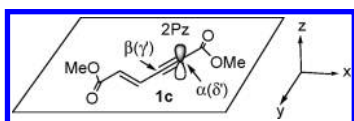
	Mulliken charge		LUMO coefficient ($2P_z$)		δ (ppm)	
entry	$\alpha(\delta')$	$\beta(\gamma')$	$\alpha(\delta')$	$\beta(\gamma')$	$\alpha(\delta')$	$\beta(\gamma')$
1[a]	−0.02	−0.06	0.21	−0.18		
2[b]	0.05	0.00	0.20	−0.15		
3[c]	0.15	0.03	0.23	−0.18		
4[d]					99.4	84.8

[a] HF/6-31(G); structure optimized with B3LYP/6-31G(d). [b] B3LYP/3-21G. [c] B3LYP/6-31G(d). [d] B3LYP/6-311G+(2d,p); structure optimized with B3LYP/6-31G(d).

The addition pattern of currently studied enyne (**1c**) can be scrutinized into two modes. **1c** is formally named hex-2-en-4-ynedioic acid dimethyl ester (IUPAC nomenclature). The reactive alkynyl carbons (the fourth and fifth carbons) are formulated at the γ,δ-position if Greek nomenclature is in compliance with the IUPAC numbering order. On the other hand, these two reactive alkynyl carbons can be regarded as α,β-carbon if we consider the alkenyl group as a substituent and designate the alkynyl carbons with Greek letters starting from its proximate ester group. Whichever these two thoughts are applied, the position of phosphine addition is inverted as compared to previous examples of alkynes with phosphines upon displacement of the alkyl to alkenyl group in alkynoates (**1a**, Scheme 1). The original definition of Michael addition[1a] states that it is the addition of a nucleophile to the β-carbon of α,β-unsaturated carbonyl compounds. Our studied enyne **1c** gives neither β-addition nor 1,4-addition with phosphine nucleophiles.

In another viewpoint, the presently studied reaction can be considered as a 1,6-nucleophilic conjugate addition at the δ' position; one may name it anti-Michael or contra-Michael addition or to a newer α-Michael addition terminology if original Michael addition equals conceptually to the broad conjugate addition.[12] Finally, the studied reactions are multicomponent reactions (MCRs)[17] with unusual addition patterns that are applicable to the preparation of useful molecules through a single reactant replacement (SRR) approach.[18] In addition, γ-lactones are core structures of many natural products,[19] for example, acetogenin gigantecin[20] and lignans.[21] Nair's previous example provided cyclopentenylphosphoranes with electron-deficient styrenes;[22] however, a combination of lactones with Wittig moiety, to the best of our knowledge, is synthetically unavailable through previous MCRs.

In summary, our findings reveal the first example of nonclassical Michael addition of phosphine nucleophiles to the $\alpha(\delta')$-position of an electron-deficient enyne. The generated dipolar intermediates react with aldehydes and form γ-lactone compounds featuring α-phosphorus ylides. This opens up a new window from which a new synthetic methodology can be utilized. Currently, we are establishing a library (sortiment) of compounds utilizing this approach with other nucleophiles, π-electrophiles, and electron-deficient alkynes in our laboratory. Further investigation of such types of lactones having Wittig moiety for application in natural products syntheses is now underway. These results will be reported in due course.

Supporting Information Available. Experimental procedures and spectral data (^{1}H, ^{31}P, and ^{13}C NMR) for compounds **4a**−**v** and X-ray crystallographic data of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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